UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
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Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/905,709	08/05/97	STERN D	5287/6/JFW/JM

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HM11/0624

EXAMINER	
LAZAR WESLEY,E	

ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 06/24/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/905,709	Applicant(s) Stern
	Examiner Eliane Lazar-Wesley	Group Art Unit 1646

☐ Responsive to communication(s) filed on _____.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

X Notice to comply /s sequence rules

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The amendment filed April 05, 1999, has been entered.

2. The rejections of claims 1-35 as being unpatentable over Neeper e tal., J.Biol.Chem. 267(1):14998-15004, July 25, 1992, in view of Schmidt et al., Artheriosclerosis and Thrombosis 14(10): 1521-1528, cited by applicants, and Bernton , US Patent 5,605,885(A), is withdrawn.

3. The rejections of claims 1-35 as being anticipated or obvious over Wautier et al., J.Clin.Invest.97(1):238-243, January 1996, is withdrawn.

Specification

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-35 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for "a polypeptide derived from soluble receptor for advanced glycation end product". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has amended claims 1 and 19 by incorporating the amino acid sequences of bovine (SEQ ID No:2) and human (SEQ ID No:4) RAGE disclosed by Neeper et al.., J.Biol.Chem. 267(1):14998-15004, July 25, 1992. However, the claims remain rejected for the reasons of record in the former Office action, page 3, because the claims are to a polypeptide *derived* from soluble receptor, and that the term derivative encompasses chemical modification, mutated forms, conjugates, etc..., and that it is unpredictable which molecule would be functional.

Applicants arguments that the specification fully enables "a polypeptide derived from soluble receptor for advanced glycation product" have been considered but have not been found persuasive, for the following reasons: Applicant argue that the specification does not have to enable every possible embodiment; while this is true, examples are only one factor used for determining enablement of an invention. Furthermore, Applicants reference to examples on page 12, lines 21 to page 13, line 1, and to page 10 starting line 11, were not persuasive and do not address the rejection, because either no example is disclosed in the cited sections, or there is no clear structural definition provided. There is no working example commensurate in scope with the unlimited number of structures

possible. Applicants argument that they provide a full description of conservative substitutions of sRAGE is not persuasive because, even though it is routine in the current state of the art to make mutants, no guidance is provided about which mutant, if any, has an activity, and it would require undue experimentation for one of skill in the art to make the invention.

Applicants include in their definition of the polypeptide of the present invention, a peptidomimetic compound (page 11, lines 1-) which may be at least partially unnatural. Considering the multitude of possible structures and not knowing what the active part of the molecule is, one of skill in the art would not know how to make and/or use the invention.

In view of the lack of guidance and of working example, and considering the breadth of the claims and the state of the prior art, it would constitute undue experimentation for one of skill in the art to make and/or use the invention.

Claims 1-35 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement "to prevent accelerated atherosclerosis in a subject predisposed thereto", or "to prevent a macrovessel disease in a subject predisposed thereto". The specification discloses an example (page 32, line 33, page 34, line 25+) of treatment of artificially induced diabetic mice with sRAGE, and an example of prevention in artificially induced diabetic mice (Figure 3), but the specification is not enabled for a method of prevention of accelerated atherosclerosis or a macrovessel disease. The example provided refers to a case of artificially induced diabetes, where the time of start of the disease is clearly known, where the evolution of the disease

is monitored, and where intervention is practiced at an early stage, like possibly a stage where the AGEs are not "sticking" to the cell walls and wherein a soluble form of RAGE can possibly "trap" the AGEs. Atherosclerosis and macrovessel diseases are usually diseases that develop over an extended period of time, that do not show symptoms for long periods of time, and for which the "starting point" is unknown. Even if numerous risk factors for atherosclerosis have been cited in the medical and scientific literature , there is no clear parameter defining who is predisposed to develop it, at which stage of their life, under which circumstances, and how and when the polypeptide should be administered. The susceptibility to atherosclerosis and macrovessel disease varies greatly among individuals exposed to identical risk factors, and it is unpredictable which individual is going to develop the disease and over which period of time. The specification does not provide guidance about how to determine who is predisposed to develop the diseases or at which stage of the disease the polypeptide should be administered. It is unpredictable if the prevention will work in an established or an advanced stage of disease, in a case of naturally occurring diabetes in human for example. It is even less predictable if the prevention method would work in other diseases where atherosclerosis and macrovessel disease are not associated specifically with diabetes, like different types of hyperlipidemia or hypothyroidism. In view of the lack of guidance and working example, considering the state of the art and that it is unpredictable who is predisposed to develop the disease and when the preventive treatment should be applied, it would constitute undue experimentation to make and/or use the invention commensurate in scope with the claims.

Applicants's arguments have been considered, but are not found persuasive for the reasons discussed above and the following ones. Applicants argue that the specification gives a full description of clinical signs, biochemical signs and hereditary disorders which would indicate that a person is predisposed to accelerated atherosclerosis. While the Examiner agrees that numerous risk factors are known (like high blood pressure, obesity) and may play a role in the development of vascular diseases, it is still unpredictable to determine who is predisposed to develop the vascular diseases (like for example which person drinking soft as opposed to hard water), and who would be prevented from developing the disease through the administration of a polypeptide derived from soluble receptor for advanced glycation product. Further, the model system used (artificially induced diabetes in mice) is not predictive of prevention in such patients, for reasons cited above.

7. Claims 1-35 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19, and their dependent claims 2-18 and 20-35, remain indefinite for the reasons of record, because they recite a "polypeptide derived from soluble receptor for advanced glycation product", without providing the metes and bounds of what is encompassed by "derived". Such term might for example encompass mutated forms, chemical modifications, conjugates, cross-linked forms, etc...

Applicant's arguments have been considered but are not found persuasive, because they do not provide structural characteristics for a "derived" polypeptide, and do not recite what is the part

of the soluble receptor that binds to AGEs and what part of the soluble receptor the derived polypeptide comes from. The specification provides a list that encompasses an unlimited number of structures to choose from (including analogs and peptidomimetic compounds which may be at least partially unnatural (page 10-11)), but does not define the metes and bounds and the structural characteristics of the derived polypeptide allowing to define the invention.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eliane Lazar-Wesley, PhD, whose telephone number is (703) 305 4059. The examiner can normally be reached on Monday-Friday from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310.

Official papers filed by fax should be directed to (703) 308 4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ELW
June 21, 1999
tw

LORRAINE SPECTOR
PRIMARY EXAMINER

Application No. 08/905,709

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.